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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/910,432	07/20/2001	Jacob Waugh	13720-105065US1	2657

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	09/910,432	WAUGH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-85,87-90,139 and 140* is/are pending in the application.

4a) Of the above claim(s) *42-65 and 68-85* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,66,67,87-90,139 and 140* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received on 7/9/09.

Claims 40-85, 87-90, 139 and 140 remain pending.

After further consideration, the rejection of the elected species of invention under 35 USC 103 over Kayyem, Yan, and Kabanov is withdrawn. The rejection depended on the suggestion in the Kayyem reference to use a fusogenic peptide in a composition similar to that claimed, and indicated that SEQ ID NO: 20 would have been obvious to use as that fusogenic peptide. However, Kayyem disclosed the use of fusogenic peptides in the context of promoting release from endosomes. There is no evidence of record that SEQ ID NO: 20 performs this particular function, and after further search of the prior art, the Examiner was unable to locate any reference suggesting that SEQ ID NO: 20 should be used for that specific purpose. Furthermore, while SEQ ID NO: 20 is an art-recognized nuclear localization signal, and Kayyem suggests the use of nuclear localization signals, there is no apparent reason to use a nuclear localization signal for delivery of botulinum toxin since the intracellular site of action of botulinum toxin is cytoplasmic, not nuclear.

Claims 42-85 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention there being no allowable generic claim. Election was made without traverse in a telephone conversation on 5/8/2008, and confirmed in the response of 11/17/08.

Claims 40, 41, 87-90, 139, and 140 are under consideration.

This Action is NON-FINAL due to a new ground of rejection not necessitated by amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 40 and 139 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kayyem et al (WO 96/11712) in view of Yan et al (US 7,008,924) and Kabanov et al (Adv. Drug Del. Rev 30: 49-610, 1998).

This rejection is made over the generic form of claims 40 and 139, not limited to any species.

Kayyem taught cell-specific delivery vehicles comprising oppositely charged polymers. In one embodiment of the invention, a delivery vehicle is provided comprising a) a first polymeric molecule having a net positive or negative charge, b) at least one second polymeric molecule having a net charge opposite that of the first polymeric molecule and complexed with the first polymeric molecule, the second polymeric molecule having attached thereto at least one cell targeting moiety, and c) at least one physiological agent attached to the first or second polymeric molecule (see Figs. 1 A and 1 B) or to a third polymeric molecule (see Fig. 1 C), wherein the third polymeric molecule, if present, has a net charge opposite that of the first polymeric molecule and

is complexed with the first polymeric molecule. See abstract; Fig. 1C; page 5, lines 3-11; and page 17, lines 5-17. The physiological agent could be a therapeutic agent that has a physiological effect on the cell to which it is delivered. See page 14, lines 20-22. In a preferred embodiment the therapeutic agent is an anticancer agent such as cyclophosphamide. See page 15, lines 5-14. Cyclophosphamide is an alkylating reagent that inhibits growth of rapidly dividing tumor cells by alkylating DNA and causing mutations during DNA replication.

Kayyem also taught that fusogenic peptides, and nuclear localization signal (NLS) peptides may be attached to the polymers to facilitate subcellular delivery to the correct compartment. See page 23, lines 15-27.

Thus Kayyem fairly taught a composition comprising a cationic polymer complexed to a plurality of anionic polymers wherein the anionic polymers comprised attached targeting agents and therapeutic agents such as cyclophosphamide. The compositions can also comprise nuclear localization peptides. Kayyem taught that the complexes should be "approximately electrically neutral, since electroneutrality is generally necessary to achieve high transfection efficiency" (page 10, lines 4-6, citing Wagner (1991)).

Kayyem did not teach composition wherein a cationic polymer was covalently attached to a plurality of amino acid sequences of SEQ ID NO: 20, and did not specify a net positive charge.

Yan taught conjugates comprising Tat-derived peptides of the sequence YGRKKRRQRRR or GGGGYGRKKRRQRRR. See; column 35, lines 22-33. Yan taught

that such Tat-derived peptides were peptide transduction domains that facilitated delivery of compounds to the nucleus. See column 35, lines 22-55.

It would have been obvious to one of ordinary skill in the art at the time of the invention to attach peptides of SEQ ID NO: 20 to the cationic polymer of Kayyem in order to facilitate nuclear delivery of cyclophosphamide. One would have been motivated to attach the peptide to the cationic polymer because the peptide is strongly cationic, and the invention of Kayyem depends on the interaction of oppositely charged polymers to form a complex. Accordingly, one of ordinary skill when deciding which polymer to attach the peptide to, would opt to place it on the like-charged cationic polymer in order to avoid interfering with the charge interaction between the cationic and anionic polymers.

Regarding the charge of the complexes, Kayyem taught that they should be "approximately electrically neutral, since electroneutrality is generally necessary to achieve high transfection efficiency". So the teaching of Kayyem appears to allow for slightly negative, slightly positive, and neutral complexes. The prior art taught that the charge of interpolyelectrolyte complexes (ionic complexes between polycationic and polyanionic macromolecules) was a result-effective variable. Kabanov reviewed interpolyelectrolyte complexes for gene delivery, i.e. complexes between polycations and polyanionic nucleic acids. Regarding net charge, Kabanov indicated that polycation/DNA complexes are soluble only if there is an excess of either DNA or polycation, so that non-stoichiometric complexes are formed, which are either negatively charged (DNA excess) or positively charged (polycation excess). The

negatively charged complexes, with an excess of plasmid DNA, are inactive in eukaryotic cells. The stoichiometric (neutral) complexes precipitate and cannot be used in pharmaceutical formulations. The cationic complexes having an excess of a polycation can be produced that are both stable in solution and transfect cells. See page 50, right column, second full paragraph.

In view of these teachings, one of ordinary skill at the time of the invention would, at a minimum, have been motivated to avoid precisely electroneutral complexes with the thermodynamically reasonable expectation that such complexes would be insoluble. It is not immediately clear that the inactivity of the negatively charged nucleic acid complexes of Kabanov would convey to negatively charged complexes of Kayyem in which the "active" ingredient is not a nucleic acid. Nonetheless, in view of teachings of Kabanov, one of ordinary skill in the art at the time of the invention would have found motivation to assay complexes that retained enough of a charge, positive or negative, to remain soluble. Further, one would have considered using a ratio of polycation to polyanion that provided positively charged particles simply because Kabanov indicated that these were soluble, stable, and active. In view of the fact that the solution to the problem of maintaining complex solubility, and activity of the drug, lay in forming a complex with either a positive or negative net charge, it would have been obvious to try either negatively or positively charged complexes because these two possibilities represent a finite number of predictable potential solutions. Finally, because the prior art showed that particle charge was a result-effective variable, it would have been obvious to optimize the charge in order to maximize activity.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 7/24/09 have been fully considered to the extent that they might apply to the new ground of rejection above, but they are not persuasive. Applicant argues that Kayyem teaches away from the proposed combination, and that the combination would render the delivery vehicles of Kayyem unsuitable for their intended purpose. The arguments are based on the position that Kayyem requires cell specific delivery, whereas the HIV Tat peptide (instant SEQ ID NO: 20) mediates non-specific cellular uptake.

Applicant's arguments are unpersuasive because even if the presence of the Tat peptide led to delivery to cells other than those targeted by the targeting moiety of Kayyem, there is no evidence that the composition would not also be delivered to targeted cells. It was clear to those of ordinary skill in the art at the time of the invention that drug delivery compositions could be administered directly to the intended site of action, e.g. intratumorally. In that case, one would reasonably expect any non-specific effect of the Tat peptide on cellular uptake to be mitigated by the high percentage of target cells in the area to which the composition was delivered. Further, the nuclear localization function of the peptide would remain advantageous in facilitating delivery of cyclophosphamide to the nucleus, it's site of activity. Accordingly, Kayyem does not teach away from the invention, and the combination of references does not result in delivery vehicles that are unsuited to delivery to tumor cells.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 40, 41, 87-90, 139, and 140 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 7-24, 30, 31, 33-50, 57, and 59-61 of copending Application No. 10/591,486. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The '486 application claims compositions comprising a biologically active protein and a carrier which comprises polymeric backbone having attached positively charged branching groups and which is present in an effective amount for transdermal delivery,

wherein the association between the carrier and the biologically active protein is non-covalent. The polymeric backbone may comprise instant SEQ ID NO: 19 or 20 (see claim 31). It is clear from the supporting specification that these compositions may contain negatively charged polymers comprising botulinum toxin and targeting agents. Thus invention as a whole was prima facie obvious.

Claims 40, 41, 87-90, 139, and 140 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7-15, 29, 68-77, and 241-249 of copending Application number 10/793,138. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The '138 application claims:

A composition comprising a biologically active protein that is not insulin, and a carrier that is present in an effective amount for transdermal delivery of the biologically active protein, wherein association between the carrier and the biologically active protein is non-covalent, wherein the carrier comprises a positively charged backbone comprising a member selected from the group consisting of polyalkyleneimine, a positively charged polypeptide, a peptoid, an electronic mimic of a polypeptide and a steric mimic of a polypeptide; wherein the positively charged backbone comprises attached positively charged branching groups that are amino acid sequences selected from the group consisting of (gly)p-RGRDDRRQRRR-(gly)q (SEQ ID NO. 3), (gly)p-YGRKKRRQRRR-

(gly)q (SEQ ID NO. 4), (gly)p-RKKRRQRRR-(gly)q (SEQ ID NO. 5), (gly)n1-(gly)n2 (SEQ ID NO. 2), gly3-arg7 (SEQ ID NO. 6), GGGRKKRRQRRR (SEQ ID NO. 7), and (gly)n3-(arg)n4 (SEQ ID NO. 1), wherein the subscripts p and q are independently an integer from 0 to 20, wherein n1 is an integer from 0 to 20 and n2 is an odd integer from about 5 to about 25, and wherein n3 is an integer from 3 to about 5 and n4 is an odd integer from about 7 to about 17.

The biologically active protein can be botulinum toxin. See claims 68-73 and 241-249. When read in view of the specification as filed, the claims embrace compositions comprising a cationic backbone and a biologically active protein that is linked to a polyanion complexed to the polycation, as well as a second polyanion comprising a targeting agent. Thus invention as a whole was prima facie obvious.

Claims 40, 41, 87-90, 139, and 140 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 7-15, 29, 68-77, and 241-249 of copending Application number 11/073,307. Although the conflicting claims are not identical, they are not patentably distinct from each other.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The '307 application claims compositions comprising a biologically active protein and a carrier which comprises polymeric backbone having attached positively charged branching groups and which is present in an effective amount for transdermal delivery, wherein the association between the carrier and the biologically active protein is non-

covalent. The polymeric backbone may comprise instant SEQ ID NO: 19 or 20 (see claim 31). It is clear from the supporting specification that these compositions may contain negatively charged polymers comprising botulinum toxin and targeting agents. Thus invention as a whole was prima facie obvious.

Response to Arguments

Applicant's request to hold the rejections in abeyance is noted. The rejection over 10/793,138 is maintained because the '138 application has the same effective filing date as the instant invention, and it's claims are broader than the instantly elected invention (i.e. it is drawn to the base invention, see MPEP 804(I)(B)(1).

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Richard Schnizer/
Primary Examiner, Art Unit 1635